

REMARKS

I. INTRODUCTION

In response to the Office Action dated October 21, 2003, and the Advisory Action dated March 4, 2004, please consider the following remarks and associated exhibits. Claims 16, 17, 22, 23, 33 and 34 have been amended and claim 36 has been added. Claims 16-20, 22-26 and 33-36 remain in the application. Re-examination and re-consideration of the application is requested.

II. CLAIM AMENDMENTS

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims, and were not required to distinguish the claims over the prior art. The amendments to the claims introduce no new matter and are fully supported by the specification as filed. The claims are primarily focused on human insulin polypeptide having an amino acid substitution at position 28 in the beta chain. Human insulin analogs having a P28D amino acid substitution in the insulin beta chain (e.g. AspB28 human insulin) or a P28K/K29P amino acid substitution in the insulin beta chain (e.g. LISPRO insulin) are disclosed for example in paragraph [0049].

III. EVIDENCE IN SUPPORT OF PATENTABILITY

Appendix A provides circular dichroism spectroscopy data with two variants of human insulin polypeptides having at least one amino acid substitution. The circular dichroism data is provided as yet another illustration of how Applicants' disclosure allows an artisan to readily assess the ability of any one insulin species to form a stable heterodimer with another insulin species without undue experimentation (circular dichroism is disclosed in paragraph [0036] of the specification). The circular dichroism data further supports the enablement of the amended claims by showing that the insulin/insulin variant heterodimer equilibrium binding constant is larger than that of the insulin variant/insulin variant homodimer.

IV. NON ART REJECTION

This request for continued examination under 37 C.F.R. §1.114 presents claims that have been amended to address the outstanding rejection under 35 U.S.C. §112, first paragraph as well as data that illustrates the enablement of the claimed subject matter.

In paper #10 the Examiner rejected claims directed all insulin heterodimers that can be formed by two insulin species where these insulin heterodimers are more stable than homodimers formed by the individual insulin species. In articulating the grounds for this rejection, the Examiner stated "neither the assay nor the disclosure gives method steps on how to predictably select complimentary first and second insulin species to yield adequate bioactive compounds" and that "[t]he undue experimentation is the fact that there is no way of knowing if the selected species will work as claimed in a stabilized heterodimeric complex."

The subject matter that resulted in the above-noted enablement rejection is not the subject matter of the current claims. Specifically, all of the claims presented above have been amended to recite heterodimers where one species in the dimeric complex is wild type human insulin (and therefore is folded in the wild type protein conformation) and the other species in the dimeric complex is a variant of human insulin polypeptide having at least one amino acid substitution (preferably at position 28 in the beta chain). The claims have been further amended to encompass only those heterodimeric complexes where the heterodimer formed by the first insulin species and the second insulin species is more stable than a homodimer formed by the second insulin species.

The claimed invention is enabled because artisans would expect insulin species encompassed by the amended claims to form the stabilized heterodimeric complexes recited in these claims. Specifically, artisans understand that the wild-type conformation of a protein controls the biological activities of that protein (e.g. its interaction with other proteins). The pertinent art teaches: (1) that the sequence of amino acid residues in proteins such as insulin determines the conformation of the protein; and (2) that a change to the size, shape, charge, hydrogen-bonding capacity or chemical reactivity of an amino acid side chain is likely to affect the conformation of the protein in some way. Such alterations in protein conformation are further known alter protein activity, typically in a detrimental way. With insulin proteins for example, Applicants' data is consistent with these general teachings in the art and not surprisingly shows that insulin dimers are most stable when both species within the complex are wild-type insulin. The data further shows that insulin dimers are least stable when both species within the complex are mutant insulin. Understandably, heterodimeric complexes comprised of at least one wild-type insulin that is in its native conformation are more stable than complexes comprised of two mutant insulins.

In view of the teachings in the art and the data provided in the specification, artisans would expected that a complex where at least one insulin monomer has the wild-type amino acid sequence

(and consequently is in the wild-type conformation) will form a dimer that is more stable than a complex formed when neither of the insulin monomers has the wild-type amino acid sequence. The claims amended therefore overcome enablement rejections based on arguments that "[t]he undue experimentation is the fact that there is no way of knowing if the selected species will work as claimed in a stabilized heterodimeric complex."

V. CONCLUSION

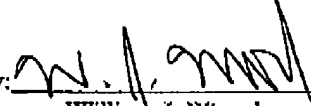
In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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